CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022150Orig1s000

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Office of Medication Error Prevention and Risk Management

Date:	June 9, 2011
Application:	NDA 022150
Through:	Melina Griffis RPh, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Anne C. Tobenkin, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name and Strength:	Firazyr (Icatibant) Injection 30 mg/3 mL (10 mg/mL)
Applicant/sponsor:	Shire Human Genetic Therapies, Inc.
OSE RCM #:	2011-1194

***** Note: This review contains proprietary and confidential information that should not be released to the public.*****

CONTENTS

EXECUTIVE SUMMARY

This review summarizes the proprietary name evaluation of Firazyr for Icatibant injection. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Our findings are consistent with the findings of the findings of the External Proprietary Name Risk Assessment submitted by the Applicant. Thus, DMEPA finds the proposed proprietary name, Firazyr, acceptable for this product.

The proposed proprietary name, Firazyr, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

This review is in response to a request from Shire Human Genetic Therapies, Inc. received April 4, 2011 for an assessment of the proposed proprietary name, Firazyr, regarding potential name confusion with other proprietary or established drug names in the usual practice setting. The Applicant has submitted container labels, carton and package insert labeling for this product which are currently undergoing analysis as a separate review, OSE review #2011-1048.

1.1 REGULATORY HISTORY

Firazyr is a pending NDA application with an anticipated action date of August 25, 2011. DMEPA evaluated the proprietary name Firazyr in OSE review #2006-749 (IND 068214) dated December 18, 2006 and in OSE review # 2007-2386 (NDA 022150) dated March 10, 2008. Both DMEPA reviews found the name acceptable.

1.2 PRODUCT INFORMATION

Firazyr (Icatibant) is a bradykinin antagonist indicated for treatment of acute attacks of hereditary angioedema (HAE) in adults. The recommended dose is 30 mg (3 mL) administered by slow subcutaneous injection in the abdominal area. Additional doses may be administered at intervals of at least 6 hours if response is inadequate or if symptoms recur. The maximum daily dosage is 3 doses. Firazyr will be available as 3 mL prefilled syringe in cartons containing one syringe or as a pack which contains three cartons. The storage per the labeling is recommended below 77 degrees Fahrenheit.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2 and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Firazyr.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'F' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to 'Firazyr', the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (one, capital letter 'F'), downstrokes (one, lower case 'z'), dotted letters (none) and cross-strokes (none). Additionally, several letters in Firazyr may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Firazyr.

When searching to identify potential names that may sound similar to Firazyr, the DMEPA staff searches for names with similar number of syllables (three), stresses (FIR-a-zyr, fir-A-zyr, fir-a-ZYR), and placement of vowel and consonant sounds. The pronunciation of Firazyr, "FIR-a-zeer", was provided by the Applicant. However, DMEPA staff take into consideration that pronunciation of parts of the name can vary (See Appendix B). Furthermore, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies (See Appendix for samples and results).

2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Applicant submitted an external evaluation of the proposed proprietary name. The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk associated with the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

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1 Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

2 Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

3 RESULTS

The following sections describe the results of the proprietary name analysis for Firazyr Injection.

3.1 DATABASE AND INFORMATION SOURCES

The DMEPA safety evaluator searches yielded a total of 20 names as having some similarity to the name Firazyr. Seventeen names (Firmagon, Feogen, Fergon, Tirazone, Feratab, Finevin, Teargen, Emcyt, Terazol, Fentanyl, Levoxyl, Staxyn, Feraplex, Tiazac, Fanapt, Fasigyn, and Fluogen) were determined to be orthographically similar to Firazyr. The remaining three names (Fabrazyme, Virazole, and Firazyr) were determined to be both phonetically and orthographically similar.

A search of the United States Adopted Name stem list on April 27, 2011 did not identify any United States Adopted Names (USAN) stem within the proposed name, Firazyr.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Firazyr.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 33 practitioners responded. Ten of the respondents interpreted the name correctly as 'Firazyr'. The patterns of misinterpretations varied depending on whether the study was written or oral. Common misinterpretations in the written studies included; 'T', 'L', or 'J' for 'F'. Common misinterpretations in the oral study included: "S", "B", or "Th" for "F", "a" for "i" and "i" for "y". See Appendix C for the complete listing of interpretations from the verbal and written prescription studies. None of the respondents misinterpreted the proposed proprietary name, Firazyr, for a proprietary name that is a currently marketed product.

3.4 EXTERNAL PROPRIETARY NAME RISK ASSESSMENTS

The April 4, 2011 submission from the Applicant included a proprietary name analysis conducted by the RxMark. RxMark found the proposed proprietary name, Firazyr, acceptable. Their study identified and evaluated a total of six names, Famvir, Fortaz, Rifadin, Rifater, Telzir, and Virazole, for potential confusion with Firazyr. DMEPA identified two of the six names (Famvir and Virazole) during our database searches. Therefore, the remaining four names were added to our analysis.

3.5 COMMENTS FROM THE DIVISION OF PULMONARY, ALLERGY AND RHEUMATOLOGY PRODUCTS (DPARP)

In response to the OSE e-mail sent April 26, 2011, the Division of Pulmonary, Allergy, and Rheumatology Products did not forward any comments or concerns on the proposed proprietary name at the initial phase of the review.

DMEPA notified DPARP via e-mail on May 11, 2011 that we have no objections to the proposed proprietary name Firazyr. Per e-mail correspondence from DPARP on May 17, 2011, they indicated they concur with our assessment of the proposed proprietary name, Firazyr.

3.6 SAFETY EVALUATOR SEARCHES

Independent searches by the primary Safety Evaluator identified seven additional names (Prezyra, Flagyl, Trizivir, Famvir, Fuzeon, (b) (4) which were thought to have some orthographic or phonetic similarity to Firazyr. Thus, a total of 31 were identified as names with some

similarity to Firazyr; 20 names from EPD, four names from the external name study, and seven names from the independent search.

4 DISCUSSION

Firazyr is the proposed proprietary name for Icatibant Injection. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Our review considered comments from the Division and DDMAC.

4.1 PROMOTIONAL ASSESSMENT

DDMAC did not have promotional concerns with the proposed name, Firazyr. DPARP and DMEPA concurred with DDMAC's assessment.

4.2 SAFETY ASSESSMENT

DMEPA evaluated 31 names for their potential similarity to the proposed proprietary name Firazyr. No other aspects of the name were identified as a potential source for error. We determined eleven (Firazyr, Tirazone, Feraplex, Fasigyn, Fluogen, Prezyra, Rifadin, Rifater, Telzir, (b) (4) and (b) (4) of the 31 names would not pose a risk for confusion for the reasons noted in Appendix E.

Failure Mode and Effects Analysis (FMEA) was then applied to determine if the proposed name, Firazyr, could potentially be confused with the remaining 20 names and lead to medication errors. This analysis determined that the name similarity between Firazyr was unlikely to result in medication errors with any of the 20 products for the reasons presented in Appendix F. This finding was consistent with and supported by the independent risk assessment of the proprietary name submitted by the Applicant.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Firazyr, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Sponsor. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Firazyr, for this product at this time.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Firazyr, and have concluded that it is acceptable.

The proposed proprietary name, Firazyr, will be re-reviewed in 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. The conclusions upon re-review are subject to change.

REFERENCES

1. Micromedex Integrated Index (*http://csi.micromedex.com****)***

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. Drug Facts and Comparisons, online version, St. Louis, MO (*http://factsandcomparisons.com****)***

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

5. Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. Drugs@FDA (*http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm****)***

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. Electronic online version of the FDA Orange Book *(http://www.fda.gov/cder/ob/default.htm)*

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U.S. Patent and Trademark Office (*http://www.uspto.gov****)***

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (*www.clinicalpharmacology-ip.com****)***

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (*www.thomson-thomson.com****)***

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (*www.naturaldatabase.com****)***

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (*www.statref.com****)***

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (*http://www.ama-assn.org/ama/pub/category/4782.html****)***

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (*www.lexi.com****)***

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. 3

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. 4 DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the

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3 National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

4 Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[5] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

5 Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

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6 Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

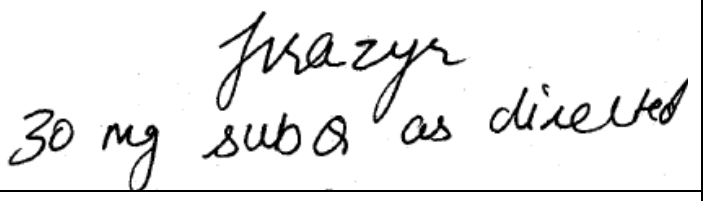
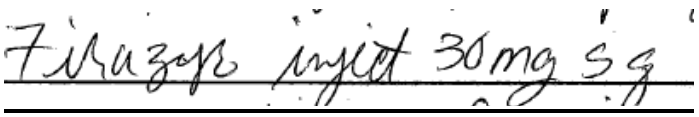
Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval

efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Firazyr	**Scripted may appear as**	**Spoken may be interpreted as**
F	T, J, L	"V", "B", "Sp", "Ph"
i	e	"ee", "ear"
r	s, n, v	
a	e, o, u	"e"
z	g, y, j	"s", "c"
y	g, z, j, p	"i"
r	s, n, v	

Appendix C: 4/29/2011 Rx Study

Handwritten Medication Order	Verbal Prescription
 	Firazyr 30 mg sub q as directed

Appendix D: FDA Prescription 4/29/2011 Study Responses

Inpatient Medication Order	Outpatient Prescription	Voice Prescription
FIRAZYR	TRAZYR	FUROZIR
FIRAZYR	TRAZYR	FURAZIR
FIRZAYR INJECT 30 MG SQ	LURAZYR	SPIRAZIR
FIRAZYR	JIRAZYR	FURAZIR
FIRAZOPR INJECTION	TRAZYR	FERAZERE
FIRAZYR	TIRAZYR	FIRAZIR
FIRAZYR	FURAZYR	FURIZIR
FIRAZYR	JISAZYR ??	BURIZIR
FIRAZYR	JURAZYR	THIRAZIR
FIRAZYR	JIRAZYR	FERAZER
FIRAZYR		FIRAZIR
FIRAZYR		

Appendix E: Names that did not undergo FMEA analysis

Name	Reason
Firazyr	Application under review
Tirazone	Name not found in frequently used databases, (Tirapazime is associated with Tirazone in Clinpharm and is also found in DARRTS (b) (4) however Tirazone is not in DARRTS)
Feraplex	Product discontinued and was only marketed in Puerto Rico
Fasigyn	Product not marketed in the U.S.
Fluogen	Product discontinued, no generic available
Prezyra	Name registered with Glaxo in USPTO, however not found in other commonly used drug databases
Rifadin	Name not orthographically or phonetically similar to Firazyr
Rifater	Name not orthographically or phonetically similar
Telzir	Product not marketed in the U.S.

(b) (4)

Appendix F: Name confusion is prevented by the combination of stated product characteristics and/or orthographic differences as described

Product name with potential for confusion	**Similarity to Proposed Proprietary Name**	**Strength and dosage form**	**Usual Dose (if applicable)**	**Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described**
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Firmagon (Degarelix)	Orthographic	80 mg or 120 mg powder for injection	Starting dose: 240 mg given as two 120 mg/3 mL subcutaneous injections followed by Maintenance dose: 80 mg/4 mL subcutaneously every 28 days	*Orthographic differences* - Firazyr has two downstrokes vs. Firmagon has one downstroke *Product characteristics* - Frequency of administration (as needed for attack vs. once a month) - Strength (30 mg/3 mL, single strength, not required on prescription vs. 80 mg or 120 mg)
Feogen (Ferrous fumarate, cyanocobala-min, Ascorbic acid)	Orthographic	66 mg/ 10 mcg/ 250 mg oral tablet	One tablet by mouth three times daily	*Orthographic differences* - Firazyr has two downstrokes vs. Feogen has one downstroke *Product characteristics* - Route of administration (subcutaneous vs. oral) - Frequency of administration (one time as needed vs. three times daily) - Dosage form (prefilled syringe vs. tablet)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Fergon (Ferrous gluconate)	Orthographic	27 mg oral tablet	One tablet by mouth every day	*Orthographic differences* - Firazyr has two downstrokes vs. Fergon has one downstroke *Product characteristics* - Route of administration (subcutaneous vs. oral) - Frequency of administration (one time as needed vs. every day) - Dosage form (prefilled syringe vs. tablet)
Feratab (Ferrous sulfate)	Orthographic	300 mg oral tablet	One tablet by mouth 3 times daily	*Orthographic differences* - Firazyr has two downstrokes vs. Feratab has no downstrokes - Firazyr has one upstroke vs. Feratab has three upstrokes *Product characteristics* - Route of administration (subcutaneous vs. oral) - Frequency of administration (once as needed vs. three times a day) - Dosage form (prefilled syringe vs. tablet)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Fineven (Azelaic acid) Discontinued, generic available	Orthographic	20% topical cream	Apply thin film to affected area in the morning and evening	*Orthographic differences* - Firazyr has two downstrokes vs. Fineven has no downstrokes *Product characteristics* - Route of administration (subcutaneous vs. topical) - Dose (one syringe vs. thin film) - Frequency of administration (once as needed vs. in the morning and evening) - Dosage form (prefilled syringe vs. cream)
Teargen (Polyvinyl alcohol)	Orthographic	1.4% ophthalmic solution	One to 2 drops in the affected eye(s) two to four times a day as needed	*Orthographic differences* - Firazyr has two downstrokes vs. Teargen has one downstroke *Product characteristics* - Route of administration (subcutaneous vs. ophthalmic) - Frequency of administration (once as needed vs. two to four times a day) - Dose (syringe vs. drop)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Emcyt (Estramustine phosphate sodium)	Orthographic	140 mg oral capsule	14 mg/kg by mouth in 3 or 4 divided doses per day	*Orthographic differences* Firazyr has one upstroke vs. Emcyt has two upstrokes - Firazyr has one upstroke vs. Emcyt has two upstrokes *Product characteristics* - Dose (one syringe vs. mg/kg weight based regimen) - Frequency of administration (once as needed vs. three to four times a day) - Route of administration (subcutaneous vs. oral) - Dosage form (prefilled syringe vs. capsule)
Terazol 7, Terazol 3 (Terconazole)	Orthographic	0.4% cream (Terazole 7) 0.7% cream (Terazole 3)	One applicatorful intravaginally at bedtime for 3 or 7 consecutive nights	*Orthographic differences* Firazyr has two downstrokes vs. Terazol has one downstroke - Firazyr has one upstroke vs. Terazol has two upstrokes *Product characteristics* - Route of administration (subcutaneous vs. vaginal) - Dose (syringe vs. applicatorful) - Strength (30 mg, single strength, not required on prescription vs. ‘3’ or ‘7’) - Frequency (once as needed vs. at bedtime) - Dosage form (prefilled syringe vs. cream)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Fentanyl	Orthographic	- 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg topical patch - 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,200 mcg buccal film, - 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg buccal tablet - 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg sublingual tablet - 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg troche - 0.05 mg/mL injection	- Apply one patch or 12.5 mcg to 100 mcg every 3 days - 200 mcg to 1200 mcg bucally every two hours as needed - 100 mcg to 800 mcg sublingually every two hours as needed - 200 mcg to 800 mcg transmucosally every two hours as needed - 50 mcg to 100 mcg intramuscular or intravenously every two hours as needed	*Orthographic differences* - Firazyr has two downstrokes vs. Fentanyl has one downstroke - Firazyr has one upstroke vs. Fentanyl has three upstrokes - Firazyr has one cross-strokes vs. Fentanyl has two cross-strokes *Product characteristics* - Strength (30 mg, single strength, not required on prescription vs. 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg, 300 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg) - Frequency of administration (one time vs. every two to four hours)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Levoxyl (Levothyroxine sodium)	Orthographic	25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg	One tablet by mouth once daily	*Orthographic differences* - Firazyr has one upstroke vs. Levoxyl has two upstrokes - Firazyr has two downstrokes vs. Levoxyl has one downstroke - Firazyr has a cross-strokes at the beginning of the name vs. Levoxyl has one cross-stroke near the end *Product characteristics* - Strength (30 mg, single strength, not required on prescription vs. 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg) - Route of administration (subcutaneous vs. oral) - Frequency of administration (one time vs. every day) - Dosage form (prefilled syringe vs. tablet)
Staxyn (Vardenafil hydrochloride)	Orthographic	10 mg orally disintegrating tablet, Blister pack containing 4 tablets	One tablet by mouth 60 minutes prior to sexual activity	*Orthographic differences* - Firazyr has one upstroke vs. Staxyn has two upstrokes - Firazyr has one cross-stroke vs. Staxyn has two cross-strokes - Firazyr has two downstrokes vs. Staxyn has one downstroke *Product characteristics* - Route of administration (subcutaneous vs. oral) - Dosage form (prefilled syringe vs. tablet)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Tiazac (Diltiazem hydrochloride)	Orthographic	120 mg, 180 mg, 240 mg, 300 mg, 360 mg, 420 mg extended-release oral capsule	120 mg to 540 mg by mouth once daily	*Orthographic differences* - Firazyr has two downstrokes vs. Tiazac has one downstroke *Product characteristics* - Strength (30 mg, single strength, not required on prescription vs. 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, 420 mg) - Route of administration (subcutaneous vs. oral) - Frequency of administration (one time vs. every day) - Dosage form (prefilled syringe vs. capsule)
Fanapt (Iloperidone)	Orthographic	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg oral tablets, available in #60 bottle and titration pack	1 mg to 12 mg by mouth twice daily	*Orthographic differences* - Firazyr has one upstroke vs. Fanapt has two upstrokes - Firazyr has two downstrokes vs. Fanapt has one downstroke - Firazyr has one cross-stroke vs. Fanapt has two cross-strokes *Product characteristics* - Strength (30 mg, single strength, not required on prescription vs. multiple strengths, 1 mg, 2mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg) - Route of administration (subcutaneous vs. oral) - Frequency (one time vs. twice daily) - Dosage form (prefilled syringe vs. tablet)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Fabrazyme (Agalsidase beta)	Orthographic and phonetic	5 mg, 35 mg powder for injection	1 mg/kg intravenous infusion every 2 weeks	*Orthographic differences* - Firazyr is seven letters vs. nine letters in Fabrazyme making it appear longer when scripted - Firazyr has one upstroke vs. Fabrazyme has two upstrokes *Phonetic differences* - Firazyr has the sound “rah” in the second syllable vs. the second syllable in Fabrazyme begins with the sound of “b” - Firazyr ends with the sound “eer” vs. “ime” in Fabrazyme *Product characteristics* - Dose (one syringe vs. 1mg/kg weight based regimen) - Frequency of administration (one time as needed vs. every two weeks) - Administration (subcutaneous vs. must be diluted and then slow intravenous infusion)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Virazole (Ribavirin)	Orthographic and phonetic	6 grams per vial	6 gram vial to be diluted and then placed in a SPAG-2 unit for conitnuous aerosol administration over 12 to 18 hours per day for 3 to 7 days	*Orthographic differences* - Firazyr has one upstroke vs. Virazole has two upstrokes - Firazyr has two downstrokes vs. Virazole has one downstroke *Phonetic differences* - Firazyr ends with the sound “eer” vs. “ahl” in Virazole *Product characteristics* - Route of administration (subcutaneous vs. inhalation) - Frequency of administration (one time vs. continuous dosing over 12 to 18 hours) - Administration (administer pre-filled syringe, no preparation required vs. must dilute in a specific machine which transforms diluted product into aerolized particles)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Flagyl (Metronida-zole)	Orthographic	375 mg oral capsule, 250 mg, 500 mg oral tablet 500 mg premixed bag	Adults: - 2 g by mouth once or 1 g by mouth twice - 250 mg, 500 mg, 750 mg by mouth three times a day - 7.5 mg/kg by mouth every 6 hours - 15 mg/kg intravenously followed by 7.5 mg/kg intravenously every 6 hours Pediatric patients: - 35 mg to 50 mg/kg by mouth divided into three daily doses	*Orthographic differences* - Firazyr has one upstroke vs. Flagyl has three upstrokes - Firazyr does not end with an upstroke vs. Flagyl ends with an upstroke *Product characteristics* - Strength (20 mg, single strength, not required on prescription) - Route of administration (subcutaneous vs. oral) - Frequency of administration (one time, as needed vs. two to three times a day, around the clock, the one time dose requires 4 capsules, thereby making the dose different)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Trizivir (Abacavir sulfate, Lamivudine, Zidovudine)	Orthographic and phonetic	300 mg/150 mg/ 300 mg oral tablet	One tablet by mouth twice daily	*Orthographic differences* - Firazyr has two downstrokes vs. Trizivir has one downstroke - Firazyr has one letter after the final downstroke vs. Trizivir has four letters after the downstroke Phonetic differences *Phonetic differences* - The first syllable in Firazyr has the sound “Fear” vs. the first syllable sound “Trihz” in Trizivir - The third syllable in Firazyr starts with the sound “zee” vs. “vee” in Trizivir *Product characteristics* - Frequency of administration (one time, as needed vs. twice daily, around the clock) - Route of administration (subcutaneous vs. oral) - Dosage form (prefilled syringe vs. tablet)
Famvir (Famciclovir)	Orthographic	125 mg, 250 mg, 500 mg oral tablet	- 1500 mg by mouth one time or 1000 mg by mouth twice daily for one day - 250 mg by mouth twice daily - 500 mg by mouth every 8 or 12 hours	*Orthographic differences* - Firazyr has two downstrokes vs. Famvir has no downstrokes *Product differences* - Strength (30 mg, single strength, not required on prescription vs. 125 mg, 250 mg, 500 mg) - Route of administration (subcutaneous vs. oral) - Dosage form (prefilled syringe vs. tablet)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength and dosage form	Usual Dose (if applicable)	Name confusion is prevented by the stated orthographic/phonetic and/or product characteristic differences as described
Firazyr (Icatibant)		**30 mg/3 mL injection, prefilled syringe**	**Inject one syringe subcutaneously as needed for attack, maximum daily dose is 3 doses**	
Fuzeon (Enfuvirtide)	Orthographic	90 mg per vial, packaged in a 30 day kit	- Adults: One syringe subcutaneously twice daily - Pediatric patients: 2 mg/kg, maximum dose, 90 mg subcutaneously twice daily	*Orthographic differences* - Firazyr has two downstrokes vs. Fuzeon has one downstroke - Firazyr has one letter after the final downstroke vs. Fuzeon has three letters after the downstroke *Product characteristics* - Frequency of administration (one time as needed vs. twice daily, around the clock) - Clinical use (Firazyr is used as a single agent vs. Fuzeon can only be used as a component of an HIV cocktail, or multi-drug therapy)
Fortaz (Ceftazadime)	Orthographic	- 1 g, 2 g pre-mixed intravenous bags - 500 mg, 1 g, 2 g, 6 g per vial	- 250 mg to 1 g intravenously or intramuscularly every 8, 12, 24 or 48 hours - 2 g intravenously every 8 to 12 hours - 30 mg to 50 mg/kg intravenously every 8 to 12 hours	*Orthographic differences* - Firazyr has one upstoke vs. Fortaz has two upstrokes - Firazyr has two downstrokes vs. Fortaz has one downstroke - Firazyr has one cross-stroke vs. Fortaz has two cross-strokes *Product characterisitcs* - Frequency of administration (one time as needed vs. every 8, 12, 24, or 48 hours around the clock) - Dose (one syringe vs. 250 mg to 1 g) - Strength (single strength, not required on prescription vs. 500 mg, 1 g, 2 g, 6 g)

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/s/

ANNE C TOBENKIN
06/09/2011

CAROL A HOLQUIST
06/09/2011

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	March 10, 2008
To:	Badrul Chowdhury, MD Director, Division of Pulmonary and Allergy Products, HFD-570
Through:	Kellie Taylor, Pharm D, MPH, Team Leader Denise Toyer, Pharm D, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention, HFD-420
From:	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Errors Prevention, HFD 420
Subject:	Proprietary Name, Label and Labeling Review for Firazyr
Drug Name:	Firazyr (Icatibant) Injection 30 mg
Application Type/Number:	NDA # 22-150
Applicant:	Jerini US Inc
OSE RCM #:	2007-2386

*** **Note: This review contains proprietary and confidential information that should not be released to the public.** ***

CONTENTS

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Firazyr, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention has no objections to the use of the proprietary name, Firazyr, for this product.

The Division of Medication Error Prevention reviewed the proposed container labels and labeling for Firazyr (Icatibant) to identify potential safety issues related to medication errors. Our analysis identified deficiencies in the way the established name is expressed, the placement of the product strength on the labels and labeling, and the potential for wrong route of administration with the proposed product design. In addition, our analysis also finds the proposed container labels and labeling introduce other vulnerabilities that could lead to medication errors. Our recommendations for label and labeling modifications are found in Section 5.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Pulmonary and Allergy Products to evaluate the proposed proprietary name for its potential to contribute to medication errors. The proprietary name, Firazyr, is evaluated to determine if the name could be potentially confused with other proprietary or established drug names. The Division of Medication Error Prevention previously reviewed and had no objection to the proprietary name, Firazyr; in OSE review # 2006-749, dated May 9, 2007.

Additionally, the container label, carton and insert labeling were provided for evaluation to identify areas that could lead to medication errors.

1.2 PRODUCT INFORMATION

Firazyr (Icatibant) injection is a bradykinin receptor type 2 antagonist for the treatment of hereditary angioedema. Firazyr is a sterile, isotonic solution packaged in prefilled syringes containing 30 mg/3 mL. It is administered as a single 30 mg subcutaneous injection which may be repeated at intervals not less than 6 hours for up to three doses in 24 hours. No more than eight doses were administered over a month during clinical trials.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. We define a medication error as any preventable event

that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Firazyr, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Firazyr, the medication error staff of the Division of Medication Error Prevention searches a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). We also conduct internal CDER prescription analysis studies, and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention uses the clinical expertise of our staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

population. Because drug name confusion can occur at any point in the medication use process, the Division of Medication Error Prevention considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'F' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4][5]

To identify drug names that may look similar to Firazyr, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (none), downstokes (two, 'z' and 'y'), cross-strokes (none), and dotted letters (one, 'i'). Additionally, several letters in Firazyr may be vulnerable to ambiguity when scripted, including the letter 'F' may appear as 'T'; lower case 'i' appear as a lower case 'e'; lower case 'r' can appear as a lower case 'n,' 'v,' or 't' ; and lower case 'z' may appear as a lower case 'g,' 'm,' or 'j'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Firazyr.

When searching to identify potential names that may sound similar to Firazyr, the Medication Error Staff search for names with similar number of syllables (three), stresses (fir-A-zeer or FIR-a-zeer), and placement of vowel and consonant sounds. In addition, several letters in Firazyr may be subject to interpretation when spoken, including the letter 'F' may be interpreted as 'Ph' or 'V'; the letter 'i' may be interpreted as 'ee' or 'eh'; the letter 'z' may be interpreted as 'c,' 's', or 'x'; or the letter 'y' as a vowel may be interpreted as an 'i' or 'e'. As such, the Staff also considers these alternate pronunciations when identifying drug names that may sound similar to Firazyr.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Firazyr), the established name (icatibant), proposed indication (hereditary angioedema), strength (30 mg), dose (30 mg), frequency of administration (single dose which may be repeated in no sooner than six hours), route (subcutaneous) and dosage form of the product (sterile solution in a prefilled syringe). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

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[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Data base and information sources

The proposed proprietary name, Firazyr, was provided to the staff of the Division of Medication Error Prevention to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Firazyr using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the Division of Medication Error Prevention to gather CDER professional opinions on the safety of the product and the proprietary name, Firazyr. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention Medication Errors Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention seeks to evaluate the potential for a proposed

[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Firazyr convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Firazyr to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].

2. The Division of Medication Error Prevention identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that the Division of Medication Error Prevention objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, the Division of Medication Error Prevention contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, the Division of Medication Error Prevention believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If we object to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. The Division of Medication Error Prevention is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[7]

Because the Division of Medication Error Prevention staff analyze reported misuse of drugs, the staff is able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on October 22, 2007 the following labels and insert labeling for the Division of Medication Error Prevention review (see Appendices H, I and J for images):

- Syringe Label: 30 mg
- Blister Label: 30 mg
- Carton Labelling: 30 mg
- Prescribing Information (no image)

The Applicant also provided the Agency a sample of the product to review on January 31, 2008.

[7] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

The Division of Medication Error Prevention conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to Firazyr to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. The USAN stem search identified no USAN stems included in this name. In total, seven names were identified as having some similarity to the name Firazyr.

Five of the seven names that were thought to look like Firazyr, which include: Famvir, Fuzeon, Finacea, Foradil, and (b) (4). One of the names, Pfizer-E, was thought to sound like Firazyr. The final name, Tera-Gel, was thought to look and sound similar to Firazyr.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention staff (see section 3.1.1. above), and noted no additional names. The Expert Panel also noted that despite orthographic similarity of the letter 'T' with the letters 'F' in some handwriting samples, few names beginning with that letters were included in the pool. In addition, Expert Panel noted that despite the phonetic match of the 'F' and 'Ph' no names beginning with that letter grouping were included in the pool. The Expert Panel recommended that independent searches consider the potential for confusion with drug names beginning with these letters or groupings.

The Expert Panel commented on the fact the product will be administered subcutaneously and the volume of the injection is 3 mL. Concerns were raised that subcutaneous injections are not usually larger than 2 mL.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 Safety evaluator risk assessment

Independent searches by the primary Safety Evaluator identified four additional names thought to look similar to Firazyr and represent a potential source of drug name confusion. The names are Furacin, Firazin, Terazosin, and Tirizin. Careful evaluation was afforded to drug names beginning with the letters 'T' and 'Ph' in accordance with the Expert Panel's recommendations. As such, a total of eleven names were analyzed to determine if the drug names could be confused with Firazyr and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Firazyr, and thus determined to present some risk of confusion. Failure mode and effect analysis was then applied to determine if the proposed name, Firazyr, could potentially be confused with any of the seven names and lead to medication errors.

*** **Note: This is proprietary and confidential information that should not be released to the public.** ***

This analysis determined that the name similarity between Firazyr and the identified names was unlikely to result in medication error for any of the eleven products identified. Two products (Firazin and Tirizin) are only marketed in foreign countries (See Appendix B). One proprietary names (b) (4) is a product that was withdrawn by the sponsor prior to the Agency acting on the application for approval. (See Appendix C.) One product, (Pfizer-E) an AB rated generic equivalent of erythromycin stearate, was withdrawn from the market in 1991. In addition, although other equivalent products continue to be marketed, the established name is routinely used in present practice settings. (See Appendix D)

For two of the eleven names identified, FMEA determined that medication errors were unlikely because the do not overlap in strength or dosage with Firazyr and have minimal orthographic and/or phonetic similarity to Firazyr (Appendix E). Four of the eleven names, like Firazyr are available in one strength leading to the omission of the strength in a prescription for the product. However, FMEA determined the products contained multiple differing product characteristics such as route of administration, frequency of administration, and prescribers which minimized the potential for confusion between these products. (See Appendix F.)

There is a potential overlap in dose of with Firazyr and the remaining name, Fuzeon, but analysis of the failure mode did not determine the effect of this similarity to result in medication errors in the usual practice setting (see Appendix G).

3.2 LABEL AND LABELING RISK ASSESSMENT

Upon review of the labels and labeling, the Division of Medication Error Prevention notes the established name does not appear to be one half the size of the proprietary name on any of the labels.

The established name for this solution is presented in the labels as (b) (4)

3.2.1 Syringe Label

We note the syringe label lacks the strength of the product.

We also note the syringe label contains no apparent expiration date.

3.2.2 Blister Label and Carton Labeling

The strength lacks prominence and is displayed away from the proprietary and established names.

The label lacks a “usual dosage” statement.

The Division of Medication Error Prevention notes the Applicant uses trailing zeros, an error prone abbreviation, to express the strength, 30 mg/ 3.0 mL, on both the blister label and carton labeling. In addition, the Applicant uses trailing zeroes in the list of active and inactive ingredients on the carton labeling.

3.2.3 Insert Labeling

The established name includes the salt (i.e., icatibant acetate) in the (b) (4) section 16 “How Supplied/Storage and Handling” of the prescribing information.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Firazyr, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

4.2 LABEL AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling appear to be vulnerable to confusion that could lead to medication errors.

4.2.1 Established name

According to regulation 21CFR 201.10(g)(2), the established name must be at least one half the size of the proprietary name. Additionally, the Applicant's proposed established name includes (b) (4) which is incongruent with the US Pharmacopeia's General Chapters Injections. The dosage form "injection" denotes a product defined by the U.S Pharmacopeia as liquid preparations that are drug substances or solutions thereof.[8] (b) (4) (b) (4) (b) (4) we believe consistent use of USP standards minimizes the potential for confusion and the risk of medication error.

4.2.2 Syringe Label

The lack of strength on the syringe label withholds necessary information from healthcare providers when administering medications. The Division of Medication Error Prevention notes the strength appears on the blister label (Appendix I). However, the prefilled syringe will be removed from the blister pack prior to administration to the patient. We note from post-marketing surveillance of medication errors that often doses of medication are prepared by one healthcare practitioner and administered by another. It is likely that the blister pack will be discarded after the syringe is removed, thus separating the strength of the product form the syringe. The healthcare practitioner will lack needed information to administer Firazyr and increase the potential for a medication error to occur.

The lack of expiration date on the syringe label also withholds necessary information from healthcare practitioners. Although the regulations provide for required information on the label when the container is too small to allow for complete labeling, we believe there is adequate space to include the expiration date as well as the strength of the product.

[8] U.S. Pharmacopeia 30, General Chapters (1) Injections. 2007

4.2.3 Blister and Carton Labeling

(b) (4)

As noted previously, the strength is necessary information healthcare providers require prior to administering a dose of any medication. Post-marketing surveillance demonstrates the inability for a healthcare practitioner to find needed information such as the strength contributes to medication errors. We believe the display of the strength near the proprietary and established names increases its prominence to the user and thus, minimizes the risk a healthcare practitioner will be unable to find this information.

The Division of Medication Error Prevention also notes required information is lacking from the labeling. According to 21CFR 201.55, a "Usual Dosage" statement is required information. Although this should not be the primary source of dosing for healthcare practitioners, we note that this information may assist healthcare practitioners in administering the correct dose. In addition, the dose is the entire 30 mg/3 mL syringe. The Division of Medication Error Prevention believes the labeling have adequate space for the "Usual Dosage" statement to list the specific dose of this product.

Trailing zeros, an error prone dose designation[9], appear on the blister and carton labeling. The Agency launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, or symbols including trailing zeroes. As part of the campaign, FDA agreed not to use such error prone designations in their approved product labeling. In general, this error-prone abbreviation creates the potential for a ten-fold dosing error when this abbreviation is carried over to prescribing and the decimal point is not readily apparent on a prescription. Additionally, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeros are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2008 National Patient Safety Goals of The Joint Commission.[10]

4.2.4 Insert Labeling

The presentation of the established name (b) (4) in several sections of the Insert labeling may potentially confuse healthcare providers. The 30 mg dose of Firazyr is based on the active moiety, icatibant. If a healthcare provider sees (b) (4) in the established name in association with the 30 mg strength, the user may attempt to recalculate the dose of icatibant. This recalculation would result in an under dosing medication error of icatibant and potentially a therapeutic failure.

4.3 OTHER MEDICATION ERROR SAFETY ISSUES

The Failure Mode and Effects Analysis review of the sample product identified potential medication error safety issues inherent its design.

[9] www.ismp.org, "ISMP's List of Error Prone Abbreviations, Symbols, and Dose Designations," The Institute of Safe Medication Practices, 2006.

[10] www.jointcommission.org, Official Do Not Use List, The Joint Commission, 2008.

The sample product demonstrates the prefilled syringe contains opportunities for medication errors to occur. The luer-lock syringe is co-packaged with the subcutaneous needle within the blister. While the route of administration appears on the labeling, the syringe label lacks this information. A healthcare provider is likely to open the blister pack containing the syringe and needle and discard the labeling leaving the healthcare provider with no information on how to administer the product.

Post-marketing surveillance of medication errors demonstrates that medications packaged in prefilled syringes have been administered incorrectly either as an intravenous or subcutaneous injection. Healthcare providers administer medications in prefilled syringes in hospitals and urgent care centers daily. These products are administered intravenously, intramuscularly or subcutaneously. The Division of Medication Error Prevention believes the Firazyr prefilled syringe has the increased potential be administered incorrectly for several reasons. First, the luer-lock syringe provides the opportunity for the product to be attached to needleless intravenous administration systems used in hospitals. In addition, the volume of the dose (3 mL) is likely to suggest to healthcare providers the dose is too large for easy subcutaneous administration reinforcing the belief the product is designed for intravenous administration. And finally, while the needle provided with the prefilled syringe is appropriate for subcutaneous administration, the potential for the short, higher gauge needle to be dropped, misplaced, or inadvertently discarded removes this signal to healthcare providers that this product is intended to be administered subcutaneously. Therefore, we believe including the route of administration on the syringe label provides a means of minimizing the potential for this product to be incorrectly administered.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Firazyr, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention does not object to the use of the proprietary name, Firazyr, for this product.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The product design of Firazyr introduces opportunities for medication errors to occur, most notably wrong route of administration. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Sponsor to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention has no objection to the proposed name, Firazyr, for this product. However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. If the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. Additionally, if the product approval is delayed beyond 90 day from the date of this review, the proposed name must be resubmitted for evaluation.

5.1.1 General Comments

1. The established name for this product requires clarification. Therefore, the Division of Medication Error Prevention recommends consulting Rik Lostritto, Chair of the Labeling and Nomenclature Committee for the appropriate expression of the established name of this product.
2. Eliminate the use of trailing zeroes, an error prone abbreviation, throughout the labels and labeling.

We recommend the revisions to the labels in Section 5.2 be implemented in the interest of minimizing user error and maximizing patient safety. We ask the recommendations in Section 5.2 be forwarded to the Applicant.

The Division of Medication Error Prevention would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Cheryl Wiseman, project manager, at 301-796-0567.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Proprietary Name

The Division of Medication Error Prevention has no objection to the proposed name, Firazyr, for this product. However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. If the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. Additionally, if the product approval is delayed beyond 90 day from the date of this review, the proposed name must be resubmitted for evaluation.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with

medication error reports involving their marketed drug products regardless of adverse event severity.

5.2.2 Labels and Labeling

5.2.2.1 General Comments

1. The Division of Medication Error Prevention recommends expressing the proprietary name, established name and strength consistently throughout the labels and labeling. For example:

Firazyr
(icatibant*) Injection
30 mg/3 mL
(10 mg/mL)
(b) (4)

2. Eliminate the use of trailing zeroes, an error prone abbreviation, throughout the labels and labeling.

5.2.2.2 Syringe Label

1. In accordance with 21CFR 201.10(g)(2), revise the font size of established name to be at least one half of the proprietary name..
2. Include the product strength (30 mg/3 mL) on the syringe label beneath the established name.
3. Include the route of administration on the syringe label.
4 Include the expiration date on the syringe label if space is available.

5.2.2.3 Blister Labeling

1. In accordance with 21CFR 201.10(g)(2), revise the font size of established name to be at least one half of the proprietary name.
2. Display the expression of the strength prominently and adjacent to the proprietary and established names.
3. Eliminate the use of trailing zeroes, an error prone abbreviation, when expressing the volume of the content of the syringe.
4. In accordance with 21CFR 201.55, the label requires revision to include a “usual dosage” statement. We recommend the statement specify the dose and the route of administration.

5.2.2.4 Carton Labeling

1. In accordance with 21CFR 201.10(g)(2), revise the font size of established name to be at least one half of the proprietary name.
2. Display the expression of the strength prominently and adjacent to the proprietary and established names.

3. In accordance with 21CFR 201.55, the label requires revision to include a "usual dosage" statement. We recommend the statement specify the dose and the route of administration.

6 REFERENCES

1. ***OSE Review # 2006-749***, Proprietary Name Review for Firazyr, Abate, R.; May 9, 2007.

2. Micromedex Integrated Index (http://weblern/)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (http://weblern/)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. Division of Medication Error Prevention proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention from the Access database/tracking system.

7. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

8. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. US Patent and Trademarks Office http://www.uspto.gov.

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (http://weblern/)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (http://weblern/)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. Stat!Ref (http://weblern/)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. the Division of Medication Error Prevention also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, the Division of Medication Error Prevention also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Downstrokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Proprietary names marketed solely in a foreign country

Proprietary Name	**Similarity to Firazyr**	**Country**
Firazin	Look and sound	Bangladesh
Tirizin	Look	Austria, Dominican Republic, and South Korea

Appendix C: Proprietary name of product that had its application withdrawn by Applicant prior to approval by the Agency.

Proprietary Name	**Similarity to Firazyr**
(b) (4)	Look

***** Note: This is proprietary and confidential information that should not be released to the public.*****

Appendix D: Proprietary names of AB rated generic product, the established name is primarily used in standard practice.

Proprietary Name	Similarity to Firazyr	Year discontinued by the manufacturer
Pfizer-E	Sound	1991

Appendix E: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Firazyr (Icatibant) injection		**30 mg prefilled syringe**	**30 mg subcutaneously once, may repeat no sooner than six hours.**
Famvir®	Look	125 mg, 250 mg, 500 mg	1000 mg once or 500 mg orally three times daily.
Terazosin	Look	1 mg, 2 mg, 5 mg, and 10 mg	1 tablet or capsule at bedtime

Appendix F: Products with a single strength but have multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose	Other differentiating product characteristics (excluding dose and frequency)
Firazyr (Icatibant) injection		**30 mg prefilled syringe**	**30 mg subcutaneously once, may repeat no sooner than six hours.**	
Finacea®	Look	15% gel	Apply twice daily	Route of administration, prescribers, and indication
Foradil®	Look	12 mcg	Inhale content of one capsule twice daily	Route of administration, prescribers, and indication
Furacin®	Look and Sound	0.2%	Apply with dressing daily	Route of administration, prescribers, and indication
Tera-Gel®	Look and Sound	0.5%	Shampoo daily, at least twice a week	Route of administration, prescribers, and indication

Appendix G: Product identified with multiple overlapping characteristics with potential for Failure mode.

Firazyr (Icatibant) injection	**30 mg prefilled syringe**	**Usual dose: 30 mg subcutaneously once, may repeat no sooner than six hours.**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Fuzeon® (Enfuvirtide) for injection 108 mg vial reconstituted solution concentration is 90 mg/mL	Orthographic similarities: begin with 'F'; contain a 'z' near the center of the name; and end with 'n' which is similar to 'r'; and have similar length. Same route of administration (subcutaneous) A 90 mg dose of Firazyr is achievable (three times 30 mg)	Orthographic differences between the names minimize the likelihood of medication error in the usual practice setting. Firazyr will be used primarily in emergency room and urgent care settings as a single dose or short series of doses, while Fuzeon is antiretroviral product used for HIV patients chronically. *Rationale:* Firazyr differs orthographically from Fuzeon as it contains a second downstroke from the 'y.' In addition, the beginning letter 'F' is separated from the 'z' by three letters in Firazyr and only one in Fuzeon. In the usual practice settings, Firazyr is utilized primarily in emergency rooms and urgent care settings as a single dose to treat an acute exacerbation of a hereditary disease, while Fuzeon is utilized by infectious disease practitioners as an ongoing treatment for HIV infections.

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